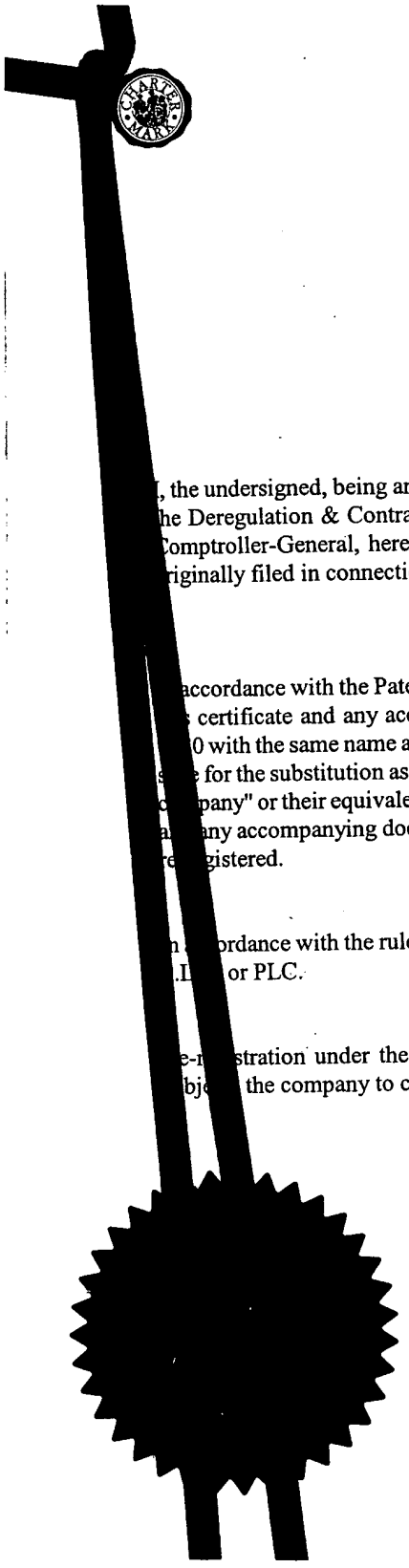

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COMPOUND

The present invention relates to a compound.

In particular the present invention relates to a compound and to a pharmaceutical composition comprising the compound.

Evidence suggests that oestrogens are the major mitogens involved in promoting the growth of tumours in endocrine-dependent tissues, such as the breast and endometrium. Although plasma oestrogen concentrations are similar in women with or without breast cancer, breast tumour oestrone and oestradiol levels are significantly higher than in normal breast tissue or blood. *In situ* synthesis of oestrogen is thought to make an important contribution to the high levels of oestrogens in tumours and therefore specific inhibitors of oestrogen biosynthesis are of potential value for the treatment of endocrine-dependent tumours.

Over the past two decades, there has been considerable interest in the development of inhibitors of the aromatase pathway which converts the androgen precursor androstenedione to oestrone. However, there is now evidence that the oestrone sulphatase (E1-STS) pathway, i.e. the hydrolysis of oestrone sulphate to oestrone (E1S to E1), as opposed to the aromatase pathway, is the major source of oestrogen in breast tumours[1,2]. This theory is supported by a modest reduction of plasma oestrogen concentration in postmenopausal women with breast cancer treated by aromatase inhibitors, such as aminoglutethimide and 4-hydroxyandrostenedione[3,4] and also by the fact that plasma E1S concentration in these aromatase inhibitor-treated patients remains relatively high. The long half-life of E1S in blood (10-12 h) compared with the unconjugated oestrogens (20 min)[5] and high levels of steroid sulphatase activity in liver and, normal and malignant breast tissues, also lend support to this theory[6].

PCT/GB92/01587 teaches novel steroid sulphatase inhibitors and pharmaceutical compositions containing them for use in the treatment of oestrone dependent tumours, especially breast cancer. These steroid sulphatase inhibitors are sulphamate esters, such as N,N-dimethyl oestrone-3-sulphamate and, preferably, oestrone-3-sulphamate (otherwise known as "EMATE").

Some of the compounds disclosed in PCT/GB92/01587 are shown in Figure 1.

It is known that EMATE is a potent E1-STS inhibitor as it displays more than 99% inhibition of E1-STS activity in intact MCF-7 cells at 0.1 μM. EMATE also inhibits the E1-STS enzyme in a time- and concentration-dependent manner, indicating that it acts as an active site-directed inactivator[7,8]. Although EMATE was originally designed for the inhibition of E1-STS, it also inhibits dehydroepiandrosterone sulphatase (DHA-STS), which is an enzyme that is believed to have a pivotal role in regulating the biosynthesis of the oestrogenic steroid androstenediol[8,9]. Also, there is now evidence to suggest that androstenediol may be of even greater importance as a promoter of breast tumour growth[10]. EMATE is also active *in vivo* as almost complete inhibition of rat liver E1-STS (99%) and DHA-STS (99%) activities resulted when it is administered either orally or subcutaneously[11]. In addition, EMATE has been shown to have a memory enhancing effect in rats[14]. Studies in mice have suggested an association between DHA-STS activity and the regulation of part of the immune response. It is thought that this may also occur in humans[15,16]. The bridging *O*-atom of the sulphamate moiety in EMATE is important for inhibitory activity. Thus, when the 3-*O*-atom is replaced by other heteroatoms (Figure 1) as in oestrone-3-*N*-sulphamate (4) and oestrone-3-*S*-sulphamate (5), these analogues are weaker non-time-dependent inactivators[12].

Although optimal potency for inhibition of E1-STS may have been attained in EMATE, it is possible that oestrone may be released during sulphatase inhibition[8,12], and that EMATE and its oestradiol congener may possess oestrogenic activity[13].

The present invention seeks to provide novel compounds suitable for the inhibition of E1-STS but preferably wherein those compounds have no, or a minimal, oestrogenic effect.

According to a first aspect of the present invention there is provided a sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound has the Formula I; wherein A is a first group; B is an aryl ring structure having at least 4 carbon atoms in the ring and wherein the ring B is substituted in at least the 2 position and/or the 4 position with an atom or group other than H; X is a sulphamate group; wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and wherein group A is attached to at least one carbon atom in ring B.

The term "sulphamate" as used herein includes an ester of sulphamic acid, or an ester of an N-substituted derivative of sulphamic acid, or a salt thereof.

The term "mimic" as used herein means having a similar or different structure but having a similar functional effect.

A key advantage of the present invention is that the sulphamate compounds of the present invention can act as E1-STS inhibitors.

Another advantage of the compounds of the present invention is that they may be potent *in vivo* and that they may have less oestrogenic activity than the known compounds and can therefore be deemed to be a "non-oestrogenic compound". The term "non-oestrogenic compound" as used herein means a compound exhibiting no or substantially no oestrogenic activity.

The present invention therefore provides sulphamate compounds which may have a reduced oestrogenic activity.

Another advantage is that the compounds may not be capable of being metabolised to compounds which display or induce hormonal activity.

The compounds of the present invention are also advantageous in that they may be orally active.

The compounds of the present invention are further advantageous in that they may have an irreversible effect.

In a preferred embodiment, the sulphamate compounds of the present invention are useful for the treatment of breast cancer.

In addition, the sulphamate compounds of the present invention are useful for the treatment of non-malignant conditions, such as the prevention of auto-immune diseases, particularly when pharmaceuticals may need to be administered from an early age.

The sulphamate compounds of the present invention are also believed to have therapeutic uses other than for the treatment of endocrine-dependent cancers, such as the treatment of autoimmune diseases.

Preferably, the sulphamate group is at position 3 of the ring B.

Preferably, the ring B has six carbon atoms in the ring.

Preferably, the compound has the Formula II; wherein X is the sulphamate group; A is the first group; R_1 and/or R_2 is a substituent other than H; wherein R_1 and R_2 may be the same or different but not both being H; and wherein optionally group A is attached to at least one other carbon atom in ring B.

Preferably, group A is additionally attached to the carbon atom at position 1 of the ring B.

Preferably, group A and ring B are a steroid ring structure or a substituted derivative thereof.

Preferably, the compound has the Formula IV; wherein X is the sulphamate group; R_1 and/or R_2 is a substituent other than H; wherein R_1 and R_2 may be the same or different but not both being H; and wherein Y is a suitable linking group.

Preferably, Y is $-CH_2-$ or -C(O)-.

Preferably, Y is -C(O)-.

Preferably, the compound has the Formula V; wherein X is the sulphamate group; R_1 and/or R_2 is a substituent other than H; and wherein R_1 and R_2 may be the same or different but not both being H.

Preferably, the sulphamate group has the Formula III; wherein each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, or together represent alkylene optionally containing one or more hetero atoms or groups in the alkylene chain.

Preferably, at least one of R_3 and R_4 is H.

Preferably, each of R_3 and R_4 is H.

Preferably, each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group.

Preferably, each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms.

Preferably, each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms.

Preferably, each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy group having from 1-6 carbon atoms.

Preferably, each of R_1 and R_2 is independently selected from H, C_3 alkyl, C_3 alkenyl, NO_2, or H_3CHO.

Preferably, the compound is any one of the Formulae V - IX.

Preferably, for some applications, the compound is further characterised by the feature that if the sulphamate group were to be substituted by a sulphate group to form a sulphate derivative, then the sulphate derivative would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity - i.e. when incubated with steroid sulphatase EC 3.1.6.2 at pH 7.4 and 37°C.

Thus, the present invention provides novel sulphamate compounds.

Preferably the group A and the ring B together - hereinafter referred to as "group A/ring B combination" - will contain, inclusive of all substituents, a maximum of about 40 carbon atoms, more usually no more than about 30.

A preferred group A/ring B combination has a steroidal ring structure, that is to say a cyclopentanophenanthrene skeleton. Preferably, the sulphamyl or substituted sulphamyl group is attached to that skeleton in the 3-position.

Thus, according to a preferred embodiment, the group A/ring B combination is a substituted or unsubstituted, saturated or unsaturated steroid nucleus.

A suitable steroid nucleus is a substituted (i.e. substituted in at least the 2 and/or 4 position and optionally elsewhere in the steroid nucleus) derivative of any one of: oestrone, 2-OH-oestrone, 2-methoxy-oestrone, 4-OH-oestrone, 6α-OH-oestrone, 7α-OH-oestrone, 16α-OH-oestrone, 16β-OH-oestrone, oestradiol, 2-OH-17β-oestradiol, 2-methoxy-17β-oestradiol, 4-OH-17β-oestradiol, 6α-OH-17β-oestradiol, 7α-OH-17β-oestradiol, 16α-OH-17α-oestradiol, 16β-OH-17α-oestradiol, 16β-OH-17β-oestradiol, 17α-oestradiol, 17β-oestradiol, 17α-ethinyl-17β-oestradiol, oestriol, 2-OH-oestriol, 2-methoxy-oestriol, 4-OH-oestriol, 6α-OH-oestriol, 7α-OH-oestriol, dehydroepiandrosterone, 6α-OH-dehydroepiandrosterone, 7α-OH-dehydroepiandrosterone, 16α-OH-dehydroepiandrosterone, 16β-OH-dehydroepiandrosterone.

In general terms the group A/ring B combination may contain a variety of non-interfering substituents. In particular, the group A/ring B combination may contain one or more hydroxy, alkyl especially lower (C_1-C_6) alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and other pentyl isomers, and n-hexyl and other hexyl isomers, alkoxy especially lower (C_1-C_6) alkoxy, e.g. methoxy, ethoxy, propoxy etc., alkenyl, e.g. ethenyl, or halogen, e.g. fluoro substituents.

The group A/ring B combination may even be a non-steroidal ring system.

A suitable non-steroidal ring system is a substituted (i.e. substituted in at least the 2 and/or 4 position and optionally elsewhere in the ring system) derivative of any one of: diethylstilboestrol, stilboestrol.

When substituted, the N-substituted compounds of this invention may contain one or two N-alkyl, N-alkenyl, N-cycloalkyl or N-aryl substituents, preferably containing or each containing a maximum of 10 carbon atoms.

When R_1 and/or R_2 and/or R_3 and/or R_4 is alkyl, the preferred values are those where each of R_1 and R_2 and R_3 and R_4 is independently selected from lower alkyl groups containing from 1 to 6 carbon atoms, that is to say methyl, ethyl, propyl etc.

When R_1 and/or R_2 and/or R_3 and/or R_4 is aryl, typical groups are phenyl and tolyl (-$PhCH_3$; *o*-, *m*- or *p*-).

Where R_1 and/or R_2 and/or R_3 and/or R_4 represent cycloalkyl, typical values are cyclopropyl, cyclopentyl, cyclohexyl etc.

When joined together R_3 and R_4 typically represent an alkylene group providing a chain of 4 to 6 carbon atoms, optionally interrupted by one or more hetero atoms or groups, e.g. -0- or -NH- to provide a 5-, 6- or 7- membered heterocycle, e.g. morpholino, pyrrolidino or piperidino.

Within the values alkyl, cycloalkyl, alkenyl and aryl we include substituted groups containing as substituents therein one or more groups which do not interfere with the sulphatase inhibitory activity of the compound in question. Examples of non-interfering substituents include hydroxy, amino, halo, alkoxy, alkyl and aryl.

We have also surprisingly found that when the compound has the Formula IV where Y = $-CH_2-$ it is not necessary for the compound to be substituted in the 2 and 4 ring positions, ie R_1 and R_2 may both be hydrogen. In one embodiment of this aspect, any of the ring positions (including R_1 and R_2, but excluding Y) may be substituted.

Thus, according to another aspect of the present invention there is provided a sulphamate compound suitable for use as an inhibitor of oestrone sulphatase wherein the compound has the Formula X and wherein X is a sulphamate group, and Y is CH_2 and optionally any other H attached directly to the ring system is substituted by another group.

X may be as described above.

Any replacement for H on the ring system may be any one of the substituents described above in relation to R_1 and R_2.

In an especially preferred embodiment there is no substitution on the ring system, ie a compound of Formula IV where Y is $-CH_2-$ and R_1 and R_2 are both H.

According to a second aspect of the present invention there is provided a sulphamate compound according to the present invention for use as a pharmaceutical.

According to a third aspect of the present invention there is provided a sulphamate compound according to the present invention for inhibiting oestrone sulphatase.

According to a fourth aspect of the present invention there is provided a pharmaceutical composition comprising a sulphamate compound according to the present invention; and a pharmaceutically acceptable carrier, excipient, adjuvant or diluent.

According to a fifth aspect of the present invention there is provided the use of a sulphamate compound according to the present invention in the manufacture of a pharmaceutical for inhibiting oestrone sulphatase.

The sulphamate compounds of the present invention may be prepared by reacting an appropriate alcohol with a sulfamoyl chloride, $R_3R_4NSO_2Cl$.

Preferred conditions for carrying out the reaction are as follows.

Sodium hydride and a sulfamoyl chloride are added to a stirred solution of the alcohol in anhydrous dimethyl formamide at 0°C. Subsequently, the reaction is allowed to warm to room temperature whereupon stirring is continued for a further 24 hours. The reaction mixture is poured onto a cold saturated solution of sodium bicarbonate and the resulting aqueous phase is extracted with dichloromethane. The combined organic extracts are dried over anhydrous $MgSO_4$. Filtration followed by solvent evaporation *in vacuo* and co-evaporated with toluene affords a crude residue which is further purified by flash chromatography.

Preferably, the alcohol is derivatised, as appropriate, prior to reaction with the sulfamoyl chloride. Where necessary, functional groups in the alcohol may be protected in known manner and the protecting group or groups removed at the end of the reaction.

For pharmaceutical administration, the steroid sulphatase inhibitors of this invention can be formulated in any suitable manner utilising conventional pharmaceutical formulating techniques and pharmaceutical carriers, adjuvants, excipients, diluents etc. and usually for parenteral administration. Approximate effective dose rates are in the range 100 to 800 mg/day depending on the individual activities of the compounds in question and for a patient of average (70Kg) bodyweight. More usual dosage rates for the preferred and more active compounds will be in the range 200 to 800 mg/day, more preferably, 200 to 500 mg/day, most preferably from 200 to 250 mg/day. They may be given in single dose regimes, split dose regimes and/or in multiple dose regimes lasting over several days. For oral administration they may be formulated in tablets, capsules, solution or suspension containing from 100 to 500 mg of compound per unit dose. Alternatively and preferably the compounds will be formulated for parenteral administration in a suitable parenterally administrable carrier and providing single daily dosage rates in the range 200 to 800 mg, preferably 200 to 500, more preferably 200 to 250 mg. Such effective daily doses will, however, vary depending on inherent activity of the active ingredient and on the bodyweight of the patient, such variations being within the skill and judgement of the physician.

For particular applications, it is envisaged that the steroid sulphatase inhibitors of this invention may be used in combination therapies, either with another sulphatase inhibitor, or, for example, in combination with an aromatase inhibitor, such as for example, 4-hydroxyandrostenedione (4-OHA).

In summation, the present invention provides novel compounds for use as steroid sulphatase inhibitors, and pharmaceutical compositions containing them.

The present invention will now be described only by way of example with reference to the accompanying drawings in which:-

Figure 1 shows the known structures of oestrone (1), oestrone sulphate (2), EMATE (3) and steroid sulphamates (4-5);

Figure 2 shows a compound of the Formula I;

Figure 3 shows a compound of the Formula II;

Figure 4 shows a compound of the Formula III;

Figure 5 shows a compound of the Formula IV;

Figure 6 shows a compound of the Formula V;

Figure 7 shows a compound of the Formula VI;

Figure 8 shows a compound of the Formula VII;

Figure 9 shows a compound of the Formula VIII;

Figure 10 shows a compound of the Formula IX;

Figure 11 shows a compound of the Formula X;

Figure 12 shows one embodiment of a method of preferring compounds of the present invention;

Figure 13 shows another embodiment of a method of preferring compounds of the present invention;

Figure 14 shows yet another embodiment of a method of preferring compounds of the present invention;

Figure 15 shows a further embodiment of a method of preferring compounds of the present invention;

Figure 16 shows a graph illustrating the *in vivo* inhibition of oestrone sulphatase by NOMATE (0.1 mg/Kg/day for five days); and

Figure 17 shows a graph illustrating the lack of effect of NOMATE (0.1 mg/Kg/day for five days) on uterine weights in ovariectomised rats.

The invention is illustrated by the following non-limiting preparative Examples and test data:

Example 1 - Preparative Methods

The preparation of various compounds in accordance with the present invention is illustrated in Figures 12 to 15.

Example 1 - *In Vitro* Inhibition

The ability of compounds on inhibit oestrone sulphatase activity was assessed using either intact MCF-7 breast cancer cells or placental microsomes as previously described[11].

The percentage inhibition for the series of EMATE analogues tested in either MCF-7 cells or placental microsomes is shown in Table 1.

Example 2 - *In Vivo* Studies

Using 17-deoxy oestrone-3-O-sulphamate (NOMATE, Figure 5, Formula IV where X = $-OSO_2NH_2$, Y = $-CH_2-$ and R_1 and R_2 = H, and Figure 13) as a representative example, the ability of this compound to inhibit oestrone sulphatase activity *in vivo* was examined in rats. The oestrogenicity of this compound was examined in ovariectomised rats. In this model compounds which are oestrogenic stimulate uterine growth.

(i) **Inhibition of oestrone sulphatase activity *in vivo***

NOMATE (0.1 mg/Kg/day for five days) was administered orally to rats with another group of animals receiving vehicle only (propylene glycol). At the end of the study samples of liver tissue were obtained and oestrone sulphatase activity assayed using ^3H oestrone sulphate as the substrate as previously described[11].

As shown in Figure 16, administration of this dose of NOMATE effectively inhibited oestrone sulphatase activity by 98% compared with untreated controls.

(ii) **Lack of *in vivo* oestrogenicity**

NOMATE (0.1 mg/Kg/day for five days) was administered orally to rats with another group of animals receiving vehicle only (propylene glycol). At the end of the study uteri were obtained and weighed with the results being expressed as uterine weight/whole body weight x 100.

As shown in Figure 17, administration of NOMATE at the dose tested, but had no significant effect on uterine growth, showing that at this dose the compound is not oestrogenic.

TABLE 1

Inhibition of Oestrone Sulphatase Activity in MCF-7 Cells or Placental Microsomes by EMATE Analogues

Inhibitor	Concentration Tested (μM)	% Inhibition (Mean) MCF-7 Cells	Placental Microsomes
2-n-propyl EMATE	0.1	41.1	-
	1	83.1	21.9
	10	92.2	43.2
	25	-	47.5
	50	-	61.1
	100	-	69.2
4-n-propyl EMATE	1	-	13.7
	10	-	10.2
	25	-	15.7
	50	-	16.3
	100	-	23.7
2,4-n-dipropyl EMATE	0.1	6.6	-
	1	10.6	-
2-allyl EMATE	0.01	23.2	-
	0.1	76.1	-
	1	94.2	45.6
	10	93.7	65.4
	25	-	75.3
	50	-	86.6
	100	-	89.6

4-allyl EMATE	1	-	29.1
(approx 75%)	10	-	54.2
	25	-	59.0
	50	-	65.1
	100	-	71.9
2,4-di-allyl EMATE	-	-	-
2-methoxy EMATE	0.1	96.0	-
	1	93.6	-
	10	96.2	99.0
	50	-	99.7
	100	-	99.7
2-nitro EMATE	0.05	-	44.5
	0.5	-	93.9
	5	-	99.0
	50	-	99.4
4-nitro EMATE	20	-	99.0
NOMATE	0.1	96.4	97.2
(17-deoxy EMATE)	1	99.1	99.5
	10	99.7	99.5
	25	99.7	99.7

- - = not tested

- Irreversible time- and concentration-dependent inhibition is assumed for these compounds in keeping with established precedent[8].

Other modifications of the present invention will be apparent to those skilled in the art.

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CLAIMS

1. A sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound has the Formula I; wherein A is a first group; B is an aryl ring structure having at least 4 carbon atoms in the ring and wherein the ring B is substituted in at least the 2 position and/or the 4 position with an atom or group other than H; X is a sulphamate group; wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and wherein group A is attached to at least one carbon atom in ring B.

2. A sulphamate compound according to claim 1 wherein the sulphamate group is at position 3 of the ring B.

3. A sulphamate compound according to claim 1 or claim 2 wherein the ring B has six carbon atoms in the ring.

4. A sulphamate compound according to any one of the preceding claims wherein the compound has the Formula II; wherein X is the sulphamate group of any one of claims 1 to 3; A is the first group according of any one of claims 1 to 3; R_1 and/or R_2 is a substituent other than H; wherein R_1 and R_2 may be the same or different but not both being H; and wherein optionally group A is attached to at least one other carbon atom in ring B.

5. A sulphamate compound according to claim 4 wherein group A is additionally attached to the carbon atom at position 1 of the ring B.

6. A sulphamate compound according to any one of the preceding claims wherein the compound has the Formula IV; wherein X is the sulphamate group of any one of claims 1 to 5; R_1 and/or R_2 is a substituent other than H; wherein R_1 and R_2 may be

the same or different but not both being H; and wherein Y is a suitable linking group.

7. A sulphamate compound according to claim 6 wherein Y is $-CH_2-$ or -C(O)-.

8. A sulphamate compound according to claim 7 wherein Y is -C(O)-.

9. A sulphamate compound according to any one of the preceding claims wherein the compound has the Formula V; wherein X is the sulphamate group of any one of claims 1 to 8; R_1 and/or R_2 is a substituent other than H; and wherein R_1 and R_2 may be the same or different but not both being H.

10. A sulphamate compound according to any one of the preceding claims wherein the sulphamate group has the Formula III; wherein each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, or together represent alkylene optionally containing one or more hetero atoms or groups in the alkylene chain.

11. A sulphamate compound according to claim 10 wherein at least one of R_3 and R_4 is H.

12. A sulphamate compound according to claim 11 wherein each of R_3 and R_4 is H.

13. A sulphamate compound according to any one of claims 4 to 12 wherein each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group.

14. A sulphamate compound according to claim 13 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms.

15. A sulphamate compound according to claim 14 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms.

16. A sulphamate compound according to claim 15 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy group having from 1-6 carbon atoms.

17. A sulphamate compound according to claim 16 wherein each of R_1 and R_2 is independently selected from H, C_3 alkyl, C_3 alkenyl, NO_2, or H_3CHO.

18. A sulphamate compound according to claim 17 wherein the compound is any one of the Formulae VI - IX.

19. A sulphamate compound according to any one of the preceding claims wherein the compound is further characterised by the feature that if the sulphamate group were to be substituted with a sulphate group to form a sulphate derivative, then the sulphate derivative would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity.

20. A sulphamate compound suitable for use as an inhibitor of oestrone sulphatase wherein the compound has the Formula X and wherein X is a sulphamate group, and Y is CH_2 and optionally any other H attached directly to the ring system is substituted

by another group.

21. A sulphamate compound according to claim 20 wherein at least one of the other H atoms attached directly to the ring system is subsituted and each substituent is independently selected from alkyl, cycloalkyl, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, an S containing group or a carboxy containing group.

22. A sulphamate compound according to claim 21 wherein each substituent is independently selected from C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, NO_2, H_3CHO or a carboxy group having from 1-6 carbon atoms.

23. A sulphamate compound according to claim 22 wherein each substituent is independently selected from C_3 alkyl or C_3 alkenyl.

24. A sulphamate compound according to claim 20 wherein none of the H atoms attached directly to the ring system is substituted.

25. A sulphamate compound according to any one of claims 20 to 24 wherein the sulphamate group has the Formula III; wherein each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, or together represent alkylene optionally containing one or more hetero atoms or groups in the alkylene chain.

26. A sulphamate compound according to claim 25 wherein at least one of R_3 and R_4 is H.

27. A sulphamate compound according to claim 26 wherein each of R_3 and R_4 is H.

28. A sulphamate compound according to any one of the preceding claims for use as a pharmaceutical.

29. A sulphamate compound according to any one of claims 1 to 27 for inhibiting oestrone sulphatase.

30. A pharmaceutical composition comprising a sulphamate compound according to any one of claims 1 to 27; and a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

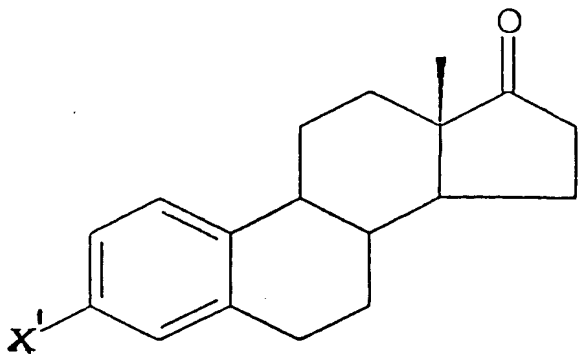
31. Use of a sulphamate compound according to any one of claims 1 to 27 in the manufacture of a pharmaceutical for inhibiting oestrone sulphatase.

32. A sulphamate compound substantially as described herein and with reference to any one of Figures 2 to 11.

ABSTRACT

COMPOUND

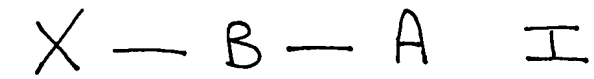
A compound is described. The compound is suitable for use as an inhibitor of oestrone sulphatase. The compound has the Formula I; wherein A is a first group; B is an aryl ring structure having at least 4 carbon atoms in the ring and wherein the ring B is substituted in at least the 2 position and/or the 4 position with an atom or group other than H; X is a sulphamate group; wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and wherein group A is attached to at least one carbon atom in ring B.



	$\underline{X'}$
(1)	-OH
(2)	$-OSO_3^-$
(3)	$-OSO_2NH_2$
(4)	$-NHSO_2NH_2$
(5)	$-SSO_2NH_2$

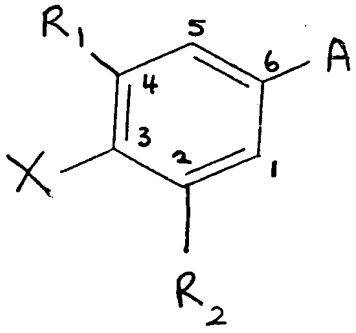
Fig 1

Fig 2



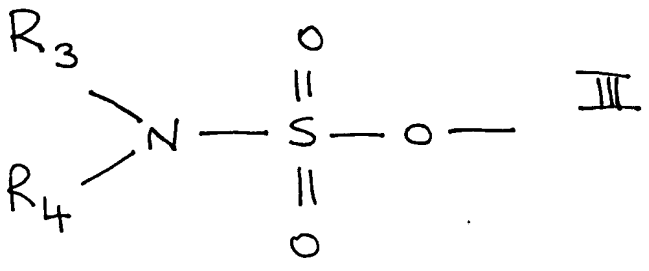
I

Fig 3

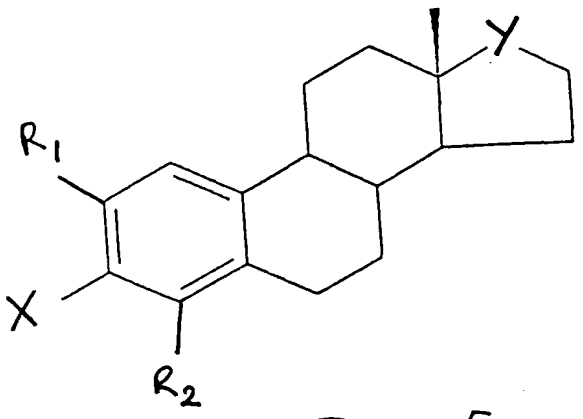


II

Fig 4

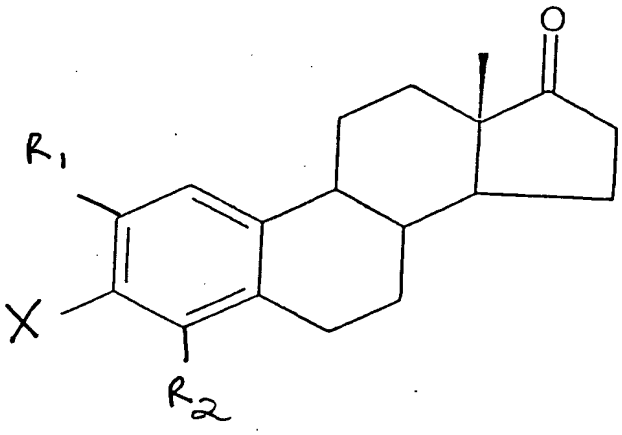


III



IV

Fig 5



V

Fig 6

VI

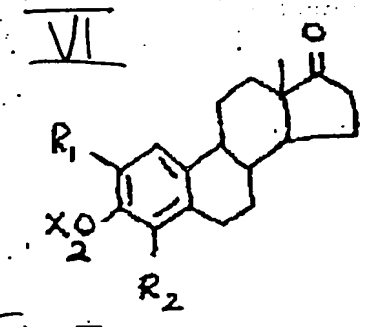


Fig 7

$X_2 = -SO_2NH_2$

	R_1	R_2
a)	n-$CH_2CH_2CH_3$	H
b)	H	n-$CH_2CH_2CH_3$
c)	n-$CH_2CH_2CH_3$	n-$CH_2CH_2CH_3$

VII

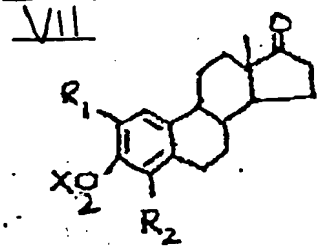


Fig 8

$X_2 = -SO_2NH_2$

	R_1	R_2
a)	$-CH_2CH=CH_2$	H
b)	H	$-CH_2CH=CH_2$
c)	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$

VIII

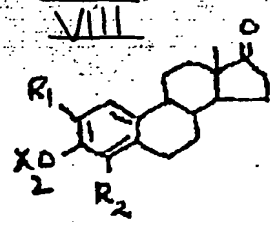


Fig 9

$X_2 = -SO_2NH_2$

	R_1	R_2
a)	H_3CO-	H
b)	H	H_3CO-
c)	H_3CO-	H_3CO-

IX

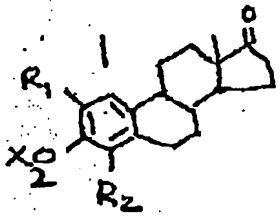
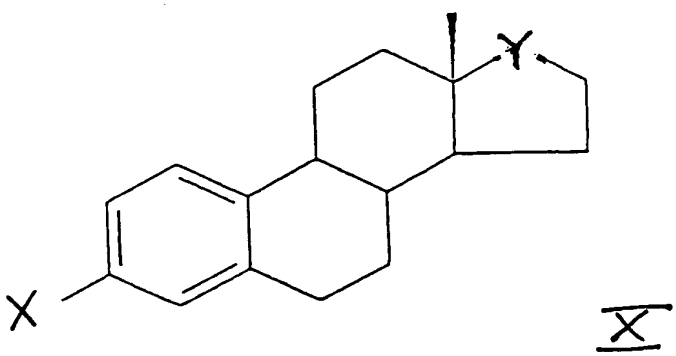


Fig 10

$X_2 = -SO_2NH_2$

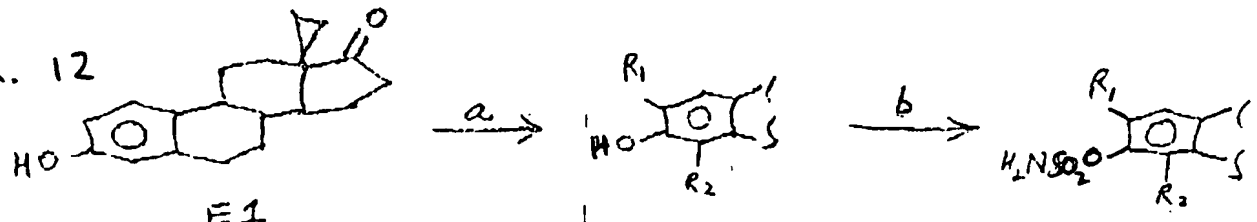
	R_1	R_2
a)	$-NO_2$	H
b)	H	$-NO_2$
c)	$-NO_2$	$-NO_2$



X

Fig. 11

FIG. 12

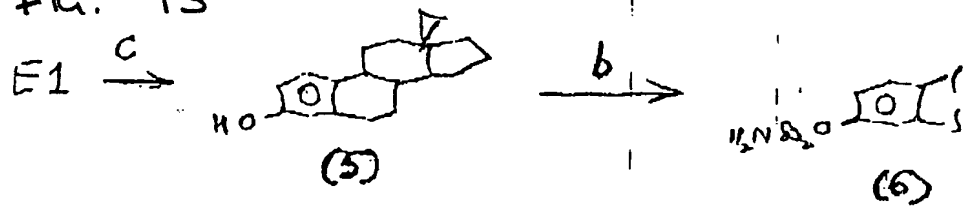


E1

	R_1	R_2
(1)	NO_2	H
(2)	H	NO_2

	R_1	R_2
(3)	NO_2	H
(4)	H	NO_2

FIG. 13



(5)

(6)

FIG. 14

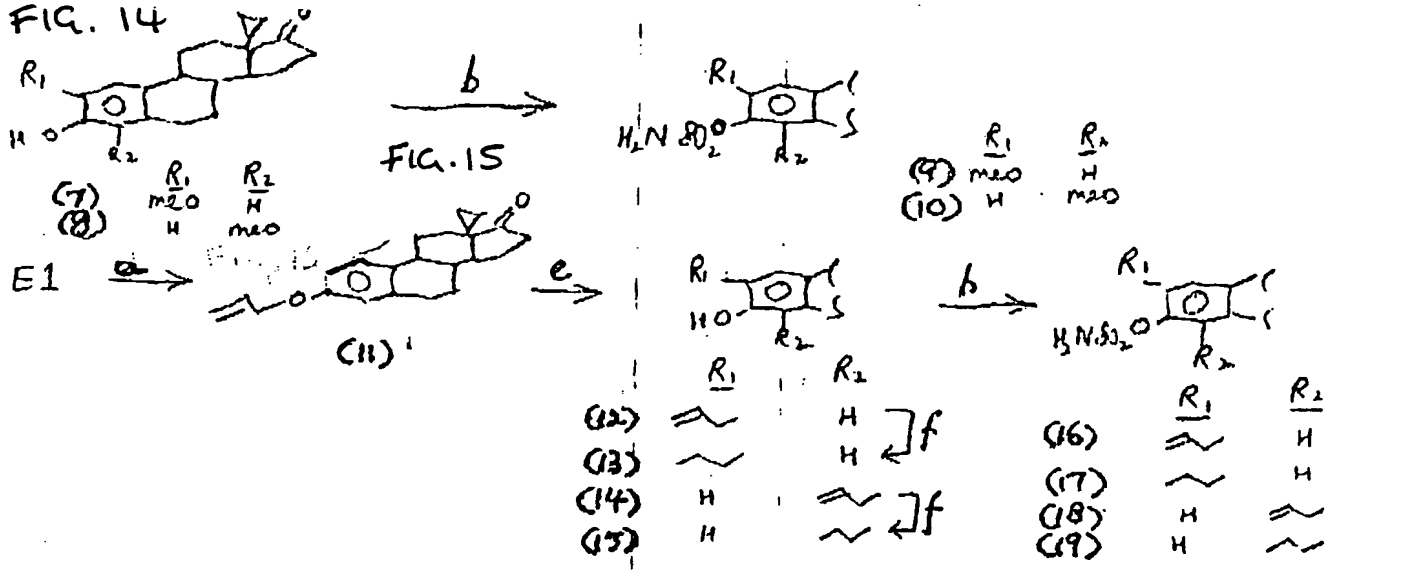


FIG. 15

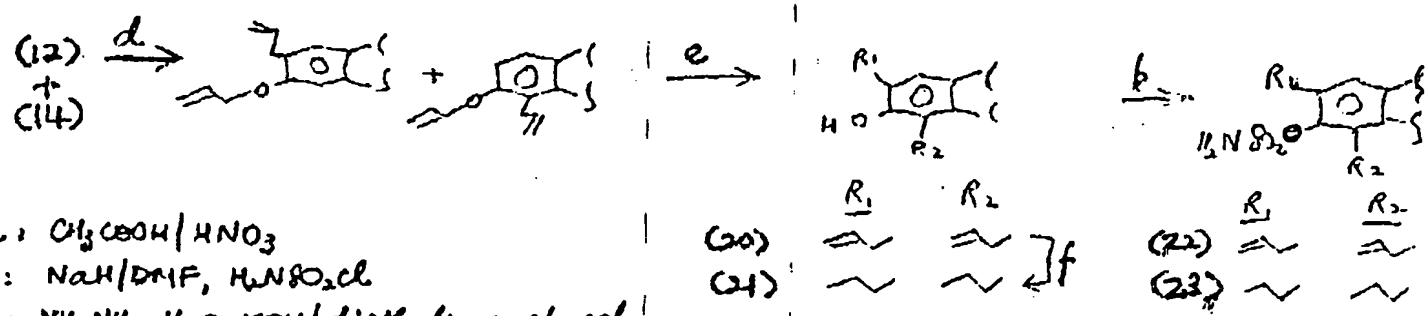
	R_1	R_2
(7)	meO	H
(8)	H	meO

	R_1	R_2
(9)	meO	H
(10)	H	meO

(11)

	R_1	R_2
(12)	≈	H
(13)	~	H
(14)	H	≈
(15)	H	~

	R_1	R_2
(16)	≈	H
(17)	~	H
(18)	H	≈
(19)	H	~



	R_1	R_2
(20)	≈	≈
(21)	~	~

	R_1	R_2
(22)	≈	≈
(23)	~	~

a: CH_3COOH/HNO_3
b: NaH/DMF, H_2NSO_2Cl
c: $NH_2NH_2 \cdot H_2O$, KOH/diethylene glycol
d: NaH/DMF, ≈Br
e: N,N-Diethylaniline, Δ
f: Pd/C, H_2

Fig. 16

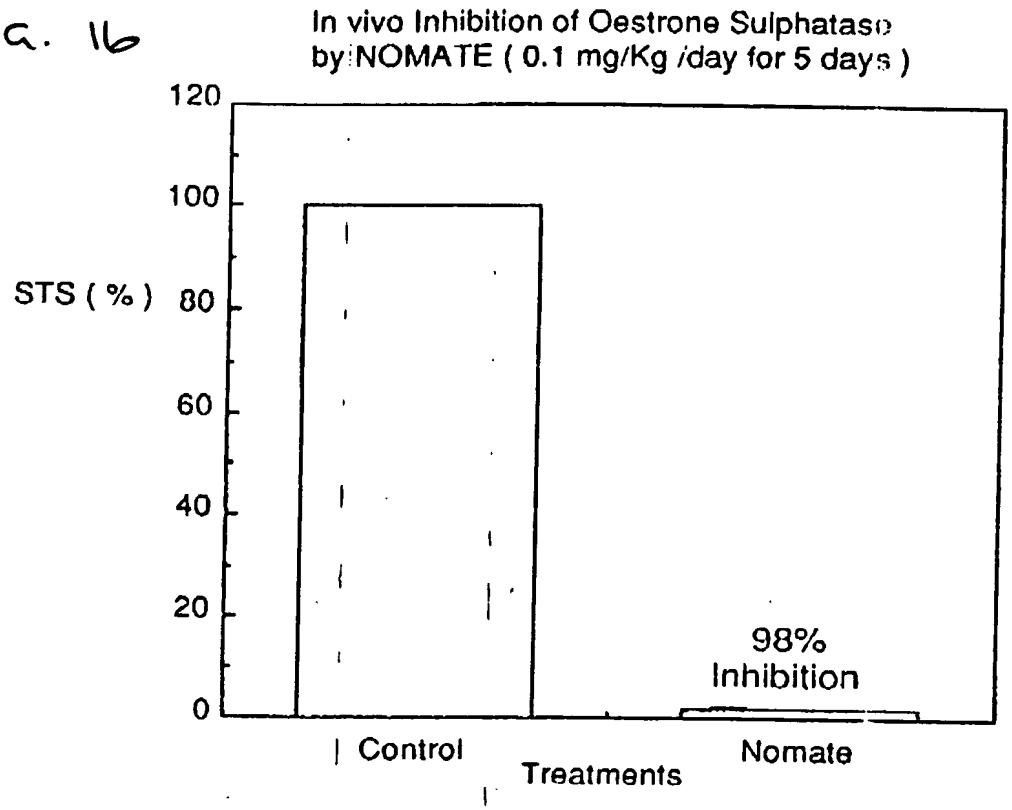
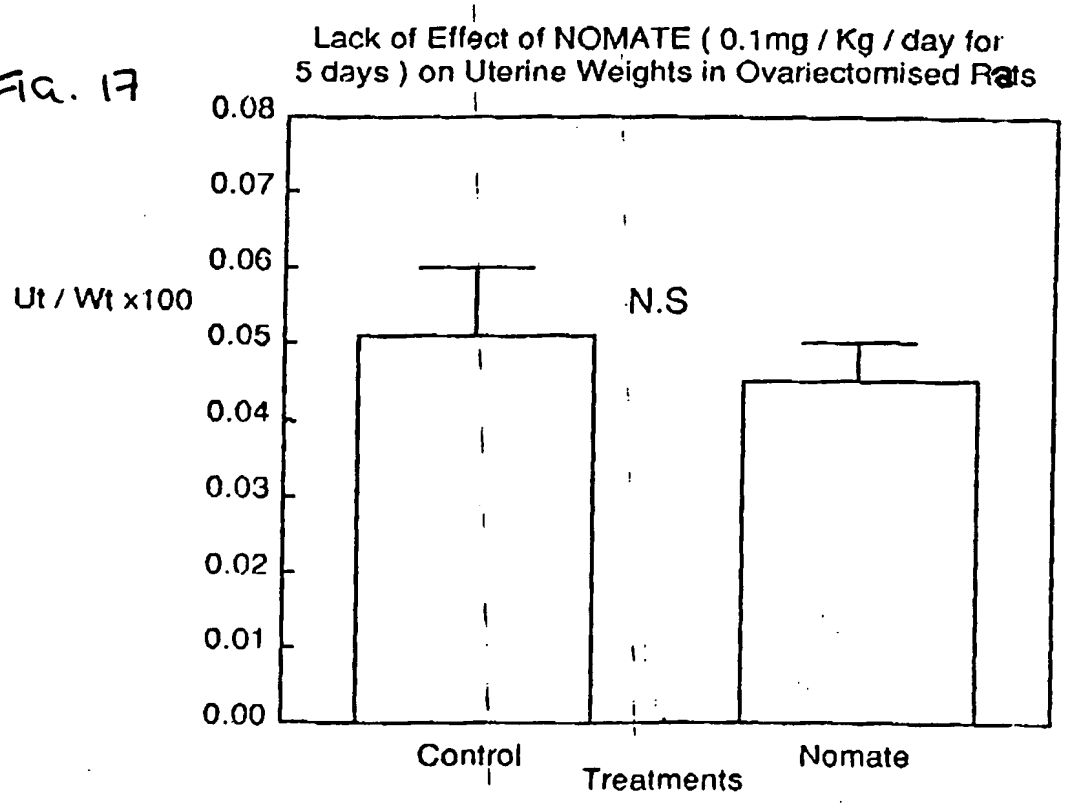

In vivo Inhibition of Oestrone Sulphatase
by NOMATE (0.1 mg/Kg /day for 5 days)
STS (%)
120
100
80
60
40
20
0
98%
Inhibition
Control
Nomate
Treatments

Fig. 17


Lack of Effect of NOMATE (0.1mg / Kg / day for
5 days) on Uterine Weights in Ovariectomised Rats
Ut / Wt x100
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
N.S
Control
Nomate
Treatments